Center for Drug Evaluation and Research
Meeting of the
Advisory Committee for Pharmaceutical Science
and
Clinical Pharmacology
August 9, 2012
Briefing Information

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package might contain assessments and/or conclusions and recommendations written by individual FDA members. Such conclusions and recommendations do not necessarily represent the final position of the individual staff member, nor do they necessarily represent the final position of any FDA office or division. We have brought the agenda items to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to any subsequent regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all relevant internal activities have been finalized. Any final determination may be affected by issues not discussed at the advisory committee meeting.

Food and Drug Administration

Meeting of the Advisory Committee for Pharmaceutical Science

and

Clinical Pharmacology

August 9, 2012

BRIEFING INFORMATION

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MEMORANDUM

TO: Members, ACPS-CP

FROM: Helen Winkle
Director, Office of Pharmaceutical Science, CDER, FDA

DATE: July 9, 2012

RE: ACPS-CP Meeting August 9, 2012

Dear Committee Members and Invited Guests,

We look forward to your participation in the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP) meeting on August 9, 2012, a continuation of the meeting of the Committee on August 8th.

The meeting will focus on a number of important science issues currently being addressed in the Office of Pharmaceutical Science (OPS) in the Center for Drug Evaluation and Research (CDER). As you know, this office is mainly focused on the review of the quality of pharmaceutical products prior to market. This includes all pharmaceutical products – small molecule and proteins, and generic versions of these products. Through your participation and advice on the advisory committee, we are able to develop and finalize our standards for reviewing and approving products and set policy for regulatory decision-making.

This meeting will focus on two specific topics. One, to start the day, will focus on current thinking on the subject of tablet scoring, and you will find this most interesting. This will be followed by further discussion on the evolving topic on nanotechnology. In both cases we will invite your discussion to assist in evaluating our current direction for these topics, and to obtain your recommendations for future activities. Background materials for each of the proposed topics are attached.

Since our last meeting, the term for a number of members has expired and new members have been appointed. We look forward to welcoming the new members and to their scientific input into the topics being brought before the committee.

We look forward to a very productive meeting on August 9th. We value the opportunity to solicit your assistance in defining and solidifying OPS direction in developing sound, scientific responses to the emerging issues.

August 9th

Topic 1 – Tablet Scoring

Over the last several years there has been a growing discussion both from within, and outside, the Agency relative to the splitting of scored tablets. These discussions have surfaced various concerns that have brought the practice of tablet splitting to the attention of CDER's Drug Safety Oversight Board at several of their recent meetings.

Accordingly, activity was begun within CDER to address these concerns. For this new topic, our current thinking will be brought to the Committee by several presentations to provide:

1. A general overview of the topic,
2. An analysis of data generated (USP Stimuli article),
3. USP's perspective on a new USP General Chapter,
4. Statistical considerations on the testing of functionally scored tablets, and
5. An overview on the published draft *Guidance for Industry*

Following the presentations, we will look forward to the Committee's discussion on the following:

Draft Discussion Points for the Committee:

1. Should the evaluation criteria require splitting by patients?
2. Should 90-day stability data be required for split sections of scored products?
3. Should friability criteria be required for split sections of scored products?
4. Should already approved/marketed scored products that do not meet the score functionality criteria outlined be allowed, or be required to remove the scoring feature?

Topic 2 – Nanotechnology – An update

This topic was previously brought before the Committee during the July 22-23, 2008, meeting of the ACPS-CP. Information presented to the Committee at that time is available at the following link: http://www.fda.gov/ohrms/dockets/ac/cder08.html#PharmScience.

Since that time there has been ongoing activity within the Center for Drug Evaluation and Research (CDER) to develop the understandings for a framework for regulatory considerations for products containing nano materials. At our current meeting we will provide an update to the Committee to cover: 1) a preliminary analysis of the data collected from submissions containing nano-scale materials, 2) a description of the risk assessment approach undertaken to evaluate the current review process and its application to products that contain nano-scale materials, and 3) a description of CDER research studies focusing on better understanding the characteristics of products containing nano-scale materials. Following the presentations, we will have Committee discussions to address the following points:

Draft Discussion Points for the Committee:

1. Does the Committee have suggestions about how to best identify products being made which are using nano materials?
2. Does the committee have suggestions about additional areas of research that CDER should be focusing on to determine the effects of using nano materials in developing and manufacturing drug products?
3. Does the Committee support the concept of the risk assessment approach and does the Committee have any recommendations for additional assessments?

We are looking forward to a very stimulating discussion with the committee on the selected topics. The meeting will be held at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Room 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002.

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (ACPS-CP)

Food and Drug Administration Campus, White Oak Conference Center
The Great Room, (Building 31, Room 1503)
Silver Spring, MD

AUGUST 9, 2012

TENTATIVE AGENDA
(SUBJECT TO CHANGE)
(Scheduled Presentation Times May Change Due to Open Public Hearing Requirements)

Thursday, August 9, 2012

8:00 a.m.	**Call to Order and Opening Remarks**	**To Be Determined**
	Introduction of Committee	
	Conflict of Interest Statement	**Yvette Waples, Pharm.D.** Designated Federal Officer
8:15 a.m.	**Welcome and Introductory Remarks**	**Helen N. Winkle** Director, Office of Pharmaceutical Science (OPS) Center for Drug Evaluation and Research (CDER), FDA
8:20 a.m.	***Topic 1: Tablet Scoring***	
10:15 a.m.	**BREAK**	
10:30 a.m.	**Open Public Hearing**	
11:00 a.m.	Topic Wrap-up and Questions to the Committee	
	Committee discussions and recommendations	
12:00 p.m.	**LUNCH**	
1:00 p.m.	***Topic 2: Nanotechnology – An Update***	
3:00 p.m.	**BREAK**	
3:15 p.m.	**Open Public Hearing**	
3:45 p.m.	Topic Wrap-up and Questions to the Committee	
	Committee discussions and recommendations	
4:30 p.m.	**Summary Comments**	
5:00 p.m.	**ADJOURNMENT**	

August 9, 2012
Topic 1

Tablet Scoring

Background Information for the FDA Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

August 9, 2012

Topic 1: *Tablet Scoring*

Historically, FDA's regulatory evaluation of scoring features – brand or generic – was not a high CMC review priority in terms of risk benefit, as tablet splitting was a fairly isolated practice. Some recent factors, however, have made tablet splitting more prevalent, to the point that CDER's Drug Safety Oversight Board considered the practice of tablet splitting at its October 2009 and November 2010 meetings. The Agency also conducted internal research on tablet scoring and found that in some cases product scoring features did not produce uniform split segments.

As an outgrowth of these discussions and developments, FDA developed draft guidance providing recommendations for application content regarding the scientific basis for scoring features on solid oral dosage form products to ensure the quality of both NDA and ANDA scored tablet products. The draft guidance describes criteria by which scored tablets can be evaluated and labeled by (1) providing a harmonized approach to chemistry, manufacturing, and controls (CMC) reviews of scored tablets; (2) ensuring consistency in nomenclature (e.g., score versus bisect) and labeling; and (3) providing information through product labeling or other means to healthcare providers. Public comments were received on the draft guidance. Tablet scoring also is addressed in pharmacopeial standards. The European Pharmacopoeia (EP) currently applies accuracy of subdivision standards for scored tablets — and has at various times also included standards for content uniformity, weight variation, and loss of mass — while the United States Pharmacopeia published a Stimuli article in 2009 (provided in the background package for your information) proposing criteria for loss of mass and accuracy of subdivision for split tablets. USP is currently considering establishing criteria for products with functional score features.

Information will be presented to the Committee to focus on following subjects:

A) Topic Introduction and Overview
B) Data Overview (USP Pharmacopeial Forum Stimuli article focus)
C) Proposed USP General Chapter -- Current Thinking and Overview
D) Testing of Functionally Scored Tablets – Statistical Considerations
E) Published FDA Draft Guidance

These efforts, comments, and proposed pathway forward will be overviewed with follow-up questions regarding guidance scope and criteria specificity.

Draft Discussion Points for the Committee:

1.) Should the evaluation criteria require splitting by patients?
2.) Should 90-day stability data be required for split sections of scored products?
3.) Should friability criteria be required for split sections of scored products?

4.) Should already approved/marketed scored products that do not meet the score functionality criteria outlined be allowed, or be required to remove the scoring feature?

Guidance for Industry

Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Russell Wesdyk at 301-796-2400.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2011
CMC

Guidance for Industry

Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2011
CMC

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Guidance for Industry[1]
Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations to sponsors of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) regarding what criteria should be met to facilitate the evaluation and labeling of tablets that have been scored. (A scoring feature facilitates the practice of tablet splitting.[2]) Specifically, this guidance recommends:

- Guidelines to follow, data to provide, and criteria to meet and detail in an application to approve a scored tablet.

- Nomenclature and labeling for approved scored tablets.

This guidance does not address specific finished-product release testing, where additional requirements may be appropriate for scored tablets.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The Agency has previously considered tablet scoring as an issue when determining whether a generic drug product is the same as the reference listed drug (RLD).[3] One characteristic of a tablet dosage form is that it may be manufactured with a score or scores. This characteristic is

[1] This guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] A score is a debossed line that runs across the planar surface of the tablet, while tablet splitting is the practice of breaking or cutting a higher-strength tablet into smaller portions.

[3] See the Manual of Policies and Procedures on *Scoring Configuration of Generic Drug Products* (5223.2), November 1, 1995.

useful because the score can be used to facilitate the splitting of the tablet into fractions when less than a full tablet is desired for a dose. Although there are no standards or regulatory requirements that specifically address scoring of tablets, the Agency recognizes the need for consistent scoring between a generic product and its RLD.

Consistent scoring ensures that the patient is able to adjust the dose, by splitting the tablet, in the same manner as the RLD. This enables the patient to switch between products made by different manufacturers without encountering problems related to the dose. In addition, consistent scoring ensures that neither the generic product nor the RLD has an advantage in the marketplace because one is scored and one is not.

CDER's Drug Safety Oversight Board considered the practice of tablet splitting at its October 2009 and November 2010 meetings.[4] During those meetings, they discussed how insurance companies and doctors are increasingly recommending that patients split tablets, either to adjust the patients' dose or as a cost-saving measure.[5] Because of this, the Agency conducted internal research on tablet splitting and concluded that in some cases, there are possible safety issues, especially when tablets are not scored or evaluated for splitting. The Agency's concerns with splitting a tablet included variations in the tablet content, weight, disintegration, or dissolution, which can affect how much drug is present in a split tablet and available for absorption. In addition, there may be stability issues with splitting tablets.[6,7]

Tablet splitting also is addressed in pharmacopeial standards. The European Pharmacopeia (EP) currently applies accuracy of subdivision standards for scored tablets—and has at various times also included standards for content uniformity, weight variation, and loss of mass—while the United States Pharmacopeia published a Stimuli article in 2009 proposing criteria for loss of mass and accuracy of subdivision for split tablets.[8]

III. DISCUSSION

As an outgrowth of these discussions and developments, we are providing recommendations for application content regarding the scientific basis for functional scores on solid oral dosage form products to ensure the quality of both NDA and ANDA scored tablet products. To accomplish

[4] Public summaries of the Drug Safety Oversight Board meetings are available at www.fda.gov/AboutFDA/CentersOffices/CDER/ucm082136.htm.

[5] It should be noted that FDA considers tablet splitting to be manufacturing under the Federal Food, Drug, and Cosmetic Act (the FD&C Act). Therefore, establishments that engage in tablet splitting must register with FDA and comply with the Agency's current good manufacturing practice (CGMP) regulations in 21 CFR parts 210 and 211. Furthermore, unless the tablet splitting is conducted pursuant to the drug product's approved labeling, the resultant split drugs are considered new drugs under the FD&C Act and, therefore, require an approved new drug application before they may be introduced into interstate commerce. However, we intend to exercise enforcement discretion and generally would not object to tablet splitting if it is performed by a pharmacist pursuant to a valid prescription for an individually identified patient.

[6] Na Zhao et al., 30 November 2010, 401(1-2), "Tablet Splitting: Product quality assessment of metoprolol succinate extended release tablets," *International Journal of Pharmaceutics.*

[7] Rakhi Shah et. al., 26 August 2010, "Tablet Splitting of a Narrow Therapeutic Index Drug: A Case with Levothyroxine Sodium," *AAPS PharmSciTech.*

[8] Geoff Green et al., November-December 2009, 35(6), "Pharmacopeial Standards for the Subdivision Characteristics of Scored Tablets," *Pharmacopeial Forum.*

this, we have developed consistent and meaningful criteria by which scored tablets can be evaluated and labeled by (1) providing a harmonized approach to chemistry, manufacturing, and controls (CMC) reviews of scored tablets; (2) ensuring consistency in nomenclature (e.g., score versus bisect) and labeling; and (3) providing information through product labeling or other means to healthcare providers.

A. Guidelines and Criteria

Below are guidelines and criteria by which a scored tablet's characteristics will be evaluated as part of the review process:

1. The dosage amount meant to be achieved after splitting the tablet should not be below the minimum therapeutic dose indicated on the approved labeling.

2. The scored dosage form should be safe to handle and not pose risk of unintended drug exposure (e.g., teratogenic, chemotherapeutic, hormones).

3. Modified release products for which the control of drug release can be compromised by tablet splitting (e.g., tablets controlled by an osmotic pump system or an exterior film coat) should not have a scoring feature.

4. The split tablet, when stored in standard high-density polyethylene pharmacy bottles and caps (no seal), should meet established stability requirements for a period of 90 days at 25º C, plus or minus 2º C/60 percent Relative Humidity (RH), plus or minus 5 percent RH.

5. The split tablet portions should meet the same finished-product testing requirements as for a whole-tablet product with equivalent strength. A risk assessment should be provided to justify the tests and criteria for product with the proposed functional score. The resulting data should be provided to the Agency for evaluation. The assessment should be undertaken on both tablets that are split nonmechanically (by hand) and tablets that are split mechanically (with a tablet splitter). Any recommended dissolution test data must be generated on a minimum of 12 individual split tablet portions.

   Below are the typical criteria, by dosage form, that should be assessed during Pharmaceutical Development (3.2.P.2.) of NDAs and ANDAs and during primary/exhibit stability batches and scale-up. As indicated above, a risk assessment should be performed to justify criteria for each product.

   a. Immediate Release Solid Oral Dosage Forms

   - USP <905> Uniformity of Dosage Units - Testing for Weight Variation is permitted for split tablet portions intended to contain 25 mg or more of a drug substance that comprises 25 percent or more (by weight) of the split tablet portion. Otherwise, the test for Content Uniformity should be used.

- Tablet splitability at both ends of the proposed hardness range should be demonstrated by:

    1. Ensuring a loss of mass of less than 3.0 percent.

    2. Confirming that the split tablet portions meet the USP Friability requirement.

- Dissolution data on split tablet portions should meet finished-product release requirements.

b. Modified Release Solid Oral Dosage Forms (Using Matrix Technology)

- All above criteria under section III.A.5.a should be met.

- Dissolution should be demonstrated at both ends of the hardness range.

- Dissolution on whole versus split tablet portions should meet the similarity factor (f2) criteria.[9]

c. Modified Release Solid Oral Dosage Forms (Using Compressed Film Coated Components)

- All above criteria under sections III.A.5.a and III.A.5.b should be met.

- Dissolution profile on pre-compressed beads versus post-compressed whole and split tablet portions should meet similarity factor (f2) criteria to ascertain the integrity of beads during compression.

6. The scored tablet should be tested using the indicated patient population to ensure patients can split the tablet correctly, as labeled.

[9] See the guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, August 1997. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

7. Scoring configuration of generic drug products should be the same as the RLD.[10]

   - Where the scoring configuration is protected by patent, contact the Office of Generic Drugs for guidance.

   - For scoring configurations proposed for abbreviated applications that were accepted through the suitability petition process, contact the Office of Generic Drugs for guidance.

8. New study data on tablet splitability should be provided during the postapproval period for any product changes at Level 2 and Level 3 as defined in the Agency's Scale-up and Post-Approval Changes (SUPAC) guidances.[11]

B. Nomenclature and Product Labeling

New products that meet the above-referenced criteria can be labeled as having a *functional score.* Such labeling should appear in all of the following sections of the prescribing information[12]:

- "Dosage Forms and Strength" section of the Highlights.
- "Dosage Forms and Strength" section of the Full Prescribing Information.
- "How Supplied" section of the Full Prescribing Information.

This information should also be included in the patient package insert or medication guide. New products that do not meet the criteria, and therefore are not approved by FDA, should not have a scoring feature or any reference to scoring (including language such as bisected, etc.) in the labeling.

For currently marketed products, manufacturers have the option to perform such an assessment and provide data for evaluation to the drug product application. Product labeling should be updated to state that it has a functional score. In this way, the use of the term *functional score* in the labeling can communicate to healthcare providers that the product has been evaluated against the established criteria.

[10] See the Manual of Policies and Procedures on *Scoring Configuration of Generic Drug Products* (5223.2), November 1, 1995, for information on what should happen if a change is made to the RLD.
[11] Go to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064979.htm for a listing of all SUPAC guidances.
[12] See 21 CFR 201.57(a)(8) and 201.57(c)(4)(ii).

August 9, 2012
Topic 2

Nanotechnology – An Update

Background Information for the FDA Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

August 9, 2012

Topic 2: ***Nanotechnology – An Update***

Following the publication of several documents on nanotechnology by the FDA, including draft guidances, MaPPs and a publication by commissioner Hamburg, the landscape of FDA's regulatory position on nanotechnology is becoming more defined. While many struggle with an official definition of "nanotechnology", FDA has articulated the principles that could be used to consider whether a product contains nanomaterials. Namely, the agency identified two questions that could be considered:

1. Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or
2. Whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects that are attributable to its dimension(s), even if these dimensions fall outside of the nanoscale range, up to one micrometer.

While a number of activities are ongoing at the agency levels, the various centers have also engaged in the development of documents aimed at better understanding the impact of nanotechnology on the regulated products. In CDER, a Manual of Policies and Practices (MaPP) was published in 2010, with the goal of developing a consistent approach in the collection of relevant data for applications containing nanomaterials. Additionally, research was undertaken to better understand products that contain nanoscale materials, such as sunscreens. Finally, a risk assessment exercise was initiated in order to optimize CDER's review process and to identify potential gaps that might be encountered during the review process.

At this advisory committee meeting CDER plans to highlight its activities in nanotechnology, namely 1) a preliminary analysis of the data collected from submissions containing nanoscale materials, 2) a description of the risk assessment approach undertaken to evaluate the current review process and its application to products that contain nanoscale materials, and 3) a description

of CDER research studies focusing on better understanding the characteristics of products containing nanoscale materials.

At the conclusion of the presentations, the Committee will be asked to consider the following questions:

1. Does the Committee have suggestions about how to best identify products being made which are using nano materials?
2. Does the committee have suggestions about additional areas of research that CDER should be focusing on to determine the effects of using nano materials in developing and manufacturing drug products?
3. Does the Committee support the concept of the risk assessment approach and does the Committee have any recommendations for additional assessments?

Useful Reference/Links for FDA Information on Nanotechnology

1. Hamburg, M., "FDA's Approach to Regulation of Nanotechnology", *Science,* vol. 236 (2012): 299-300.

2. http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm

3. http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm301114.htm

Guidance for Industry

Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All comments should be identified with the docket number (FDA-2010-D-0530) listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact:

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U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner

June 2011

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Guidance for Industry[1]
Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended for manufacturers, suppliers, importers and other stakeholders. The guidance describes FDA's current thinking on whether FDA-regulated products[2] contain nanomaterials or otherwise involve the application of nanotechnology.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. SCOPE

This guidance document does not establish any regulatory definitions. Rather, it is intended to help industry and others identify when they should consider potential implications for regulatory status, safety, effectiveness, or public health impact that may arise with the application of nanotechnology in FDA-regulated products. Public input on the guidance may also inform the development of any regulatory definitions in the future, as needed.

Nor does this guidance document address the regulatory status of products that contain nanomaterials or otherwise involve the application of nanotechnology, which are currently addressed on a case-by-case basis using FDA's existing review processes.

[1] The points to consider presented in this guidance have been prepared by the U.S. Food and Drug Administration's Nanotechnology Task Force (Task Force). The Task Force, formed in August 2006, was charged with determining regulatory approaches that would enable the continued development of innovative, safe, and effective FDA-regulated products that use nanoscale materials.

[2] The use of the word "products" in this guidance document is meant to include products, materials, ingredients and other substances regulated by FDA.

The application of nanotechnology may result in product attributes that differ from those of conventionally-manufactured products, and thus may merit examination. However, FDA does not categorically judge all products containing nanomaterials or otherwise involving application of nanotechnology as intrinsically benign or harmful.

In the future, FDA may issue additional guidance documents to address considerations for specific products or classes of products, consistent with the "Principles for Regulation and Oversight of Emerging Technologies" released March 11, 2011 as well as the "Policy Principles for the U.S. Decision-Making Concerning Regulation and Oversight of Applications of Nanotechnology and Nanomaterials" released on June 9, 2011, that were issued jointly by the Office of Science and Technology Policy, Office of Management and Budget, and the United States Trade Representative[3]

III. DISCUSSION

FDA has not to date established regulatory definitions of "nanotechnology," "nanoscale" or related terms.[4] However, there are numerous definitions of "nanotechnology." The term is perhaps most commonly used to refer to the engineering (i.e., deliberate manipulation, manufacture or selection) of materials that have at least one dimension in the size range of approximately 1 to 100 nanometers. For example, the National Nanotechnology Initiative Program defines nanotechnology as "the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications."[5] Other factors such as function, shape, charge, the ratio of surface area to volume, or other physical or chemical properties have also been mentioned in various published definitions.

As a first step toward developing FDA's framework for considering whether FDA-regulated products include nanomaterials or otherwise involve nanotechnology, the agency has developed the points discussed below. Based on FDA's current scientific and technical understanding of nanomaterials and their characteristics, FDA believes that evaluations of safety, effectiveness or

[3] http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/Principles-for-Regulation-and-Oversight-of-Emerging-Technologies-new.pdf ; http://www.whitehouse.gov/sites/default/files/omb/inforeg/for-agencies/nanotechnology-regulation-and-oversight-principles.pdf

[4] In the 2007 Report, the FDA Nanotechnology Task Force stated: "The Task Force believes FDA should continue to pursue regulatory approaches that take into account the potential importance of material size and the evolving state of the science. Moreover, while one definition for "nanotechnology," "nanoscale material," or related term or concept may offer meaningful guidance in one context, that definition may be too narrow or broad to be of use in another. Accordingly, the Task Force does not recommend attempting to adopt formal, fixed definitions for such terms for regulatory purposes at this time. As FDA learns more about the interaction of nanoscale materials with biological systems and generalizable concepts that can inform the agency's judgment, it may be productive to develop formal, fixed definitions, appropriately tailored to the regulation of nanoscale materials in FDA-regulated products" (Nanotechnology. A Report of the U.S. Food and Drug Administration Nanotechnology Task Force, July 25, 2007, page 6-7; available online at: http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm).

[5] National Nanotechnology Initiative Website, http://www.nano.gov/nanotech-101/what

public health impact of such products should consider the unique properties and behaviors that nanomaterials may exhibit.

These points to consider are intended to be broadly applicable to all FDA-regulated products, with the understanding that additional guidance may be articulated for specific product areas, as appropriate in the future.

A. Points to Consider

At this time, when considering whether an FDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology, FDA will ask:

1. Whether an engineered material or end product has at least one dimension in the nanoscale range (approximately 1 nm to 100 nm); or
2. Whether an engineered material or end product exhibits properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer.

These considerations apply not only to new products, but also may apply when manufacturing changes alter the dimensions, properties, or effects of an FDA-regulated product or any of its components. Additionally, they are subject to change in the future as new information becomes available, and to refinement in future product-specific guidance documents.

B. Rationale for Elements within the Points to Consider

1. Engineered material or end product

This term is used to distinguish between products that have been engineered to contain nanoscale materials or involve the application of nanotechnology from those products that contain incidental or background levels of nanomaterials or those that contain materials that naturally occur in the nanoscale range. FDA is particularly interested in the *deliberate* manipulation and control of particle size to produce specific properties, because the emergence of these new properties or phenomena may warrant further evaluation. This is distinct from the more familiar use of biological or chemical substances that may naturally exist at small scales, including at the nanoscale, such as microorganisms or proteins.

2. At least one dimension in the nanoscale range (approximately 1 nm to 100 nm)

A size range of approximately 1 nm to 100 nm is commonly used in various working definitions or descriptions proposed by the regulatory and scientific community.[6] In this size range,

[6] For example, a size range of approximately 1 nm to 100 nm is used in definitions, working definitions, or descriptions published by the National Nanotechnology Initiative; Environmental Protection Agency; European Scientific Committee on Consumer Products; European Commission; Health Canada; International Standards Organization; Organization for Economic Cooperation and Development's Working Party on Nanotechnology and Working Party on Manufactured Nanomaterials; National Cancer Institute; and American National Standards Institute.

materials can exhibit new or altered physicochemical properties which enable novel applications.[7] Accordingly, a range of approximately 1 nm to 100 nm should be applied as a first reference point in considering whether an FDA-regulated product contains nanomaterials or otherwise involves application of nanotechnology.

3. Exhibits properties or phenomena . . . that are attributable to its dimension(s)

These terms are used because properties and phenomena of materials at the nanoscale enable applications that can the affect safety, effectiveness, performance, quality and, where applicable, public health impact of FDA-regulated products. For example, dimension-dependent properties or phenomena may be used for functional effects such as increased bioavailability, decreased dosage, or increased potency of a drug product[8], decreased toxicity of a drug product[9], better detection of pathogens[10], enhanced protection offered by improved food packaging materials[11], or improved delivery of a functional ingredient or a nutrient in food[12]. The properties and phenomena may be due to altered chemical, biological, or magnetic properties, altered electrical or optical activity, increased structural integrity, or other unique characteristics of nanoscale materials not normally observed in their larger counterparts.[13] These changes may raise questions about the safety, effectiveness, performance, quality or public health impact of the products. In addition, considerations such as routes of exposure, dosage, and behavior in various biological systems (including specific tissues and organs) are critical for evaluating the wide array of products under FDA's jurisdiction.

4. Size range of up to one micrometer (1,000 nm)

Materials or end products can also exhibit properties or phenomena attributable to a dimension(s) above the approximate 100 nm range. A reduction in size can lead to properties that are clearly different from those of the conventionally-scaled material although the material or end product itself may not necessarily be within the nanoscale range. Structures such as agglomerates and aggregates are of interest in this context[14] as are coated, functionalized, or hierarchically

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[7] National Nanotechnology Initiative Website, http://www.nano.gov/nanotech-101/what; Powers KW, Brown SC, Krishna VB, et al. Research Strategies for Safety Evaluation of Nanomaterials. Part VI. Characterization of Nanoscale Particles for Toxicological Evaluation. Toxicological Sciences 90: 296–303, 2006.

[8] Merisko-Liversidge EM and Liversidge GG. Drug nanoparticles: formulating poorly water-soluble compounds. Toxicologic Pathology, 36:43-48, 2008.

[9] Paciotti GF, Myer L, Weinreich D, et al. Colloidal gold: a novel nanoparticle vector for tumor directed drug delivery. Drug Delivery, 11:169-183, 2004.

[10] Kaittanis C, Santra S, Manuel PJ. Emerging nanotechnology-based strategies for the identification of microbial pathogenesis. Advanced Drug Delivery Reviews 62:408-423, 2010.

[11] Chaudhry Q, Scotter M, Blackburn J, et al. Applications and implications of nanotechnologies for the food sector. Food Additives and Contaminants 25:241-258, 2008.

[12] IOM (Institute of Medicine). Nanotechnology in food products: Workshop Summary. Washington, DC: The National Academies Press, 2009; Chen L, Remondetto GE, Subirade M. Food protein-based materials as nutraceutical delivery systems. Trends in Food Science & Technology 17:272-283, 2006.

[13] Nanotechnology. A Report of the U.S. Food and Drug Administration Nanotechnology Task Force, July 25, 2007; available online at: http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/NanotechnologyTaskForceReport2007/default.htm).

[14] Considerations on a Definition of Nanomaterial for Regulatory Purposes, Joint Research Centre, 2010; available online at: http://ec.europa.eu/dgs/jrc/downloads/jrc_reference_report_201007_nanomaterials.pdf.

assembled structures[15]. To account for such materials, some definitions of nanomaterial have applied the 100 nm upper dimension to the *internal* structure[16]. In the absence of a bright line as to where an upper limit should be set, the agency considers that an upper bound of one micrometer (i.e., 1,000 nm) would serve as a reasonable parameter for screening materials with dimensions beyond the nanoscale range for further examination to determine whether these materials exhibit properties or phenomena attributable to their dimension(s) and relevant to nanotechnology.[17] The agency believes that the one micrometer upper limit in the second point to consider serves both to (1) exclude macro-scaled materials that may have properties attributable to their dimension(s) but are not likely relevant to nanotechnology; and (2) include those materials (such as aggregates, agglomerates, or coated, functionalized, or hierarchically assembled structures) with dimension(s) above 100 nm that may exhibit dimension-dependent properties or phenomena relevant to nanotechnology and distinct from those of macro-scaled materials.

IV. CONCLUSION

There is a critical need to learn more about the potential role and importance of dimensions in the characteristics exhibited by engineered nanomaterials that may be used in producing products regulated by FDA. Premarket review, when required, offers an opportunity to better understand the properties and behavior of products that contain engineered nanomaterials or otherwise involve application of nanotechnology. And where products applying nanotechnology are not subject to premarket review, the agency urges manufacturers to consult with the agency early in the product development process. In this way, any questions related to the regulatory status, safety, effectiveness, or public health impact of these products can be appropriately and adequately addressed.

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[15] Scientific Basis for the Definition of the Term "Nanomaterial", Scientific Committee on Emerging and Newly Identified Health Risks, July 6, 2010; available online at: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_030.pdf.

[16] ISO Technical Specification on Nanotechnologies – Vocabulary – Part 1: Core terms (ISO/TS 80004-1:2010); European Commission draft recommendation on the definition of the term "nanomaterial" (October, 2010).

[17] Including materials of interest with dimension(s) beyond 100 nm is consistent with the recent conclusions presented by the Joint Research Centre and the Scientific Committee on Emerging and Newly Identified Health Risks of the European Commission: "In order to base a nanomaterials definition for regulatory purposes on size alone, the upper nanoscale limit should ideally be high enough to capture all types of materials that would need particular attention for regulation due to their nanoscale size. Upper limits which are often used in existing definitions, for example 100 nm, may require the introduction of one or more qualifiers based on structural features or properties other than size, in order to capture structures of concern (for example agglomerates or aggregates) with a size larger than 100 nm in the regulation" (Considerations on a Definition of Nanomaterial for Regulatory Purposes, Joint Research Centre, 2010); "The upper size limit for one or more external dimensions of 100 nm is complicated by the potential exclusion of aggregates, agglomerates and multicomponent assemblies that would have external sizes greater than this" (Scientific Basis for the Definition of the Term "Nanomaterial", Scientific Committee on Emerging and Newly Identified Health Risks, July 6, 2010); "An upper limit of 100 nm is commonly used by general consensus but there is no scientific evidence to qualify the appropriateness of this value (Stated as SCENIHR conclusions in the EC draft recommendation on the definition of term "nanomaterial", October 2010; available online at: http://ec.europa.eu/environment/consultations/pdf/recommendation_nano.pdf). In addition, ISO "acknowledged that health and safety considerations associated with intentionally produced and incidental nano-objects do not abruptly end at dimensions of 100 nm" (ISO/TS 80004-1:2010).

OFFICE OF PHARMACEUTICAL SCIENCE

Reporting Format for Nanotechnology-Related Information in CMC Review

CONTENTS

PURPOSE

- This MAPP provides chemistry, manufacturing, and controls (CMC) reviewers within the Office of Pharmaceutical Science (OPS) with the framework by which relevant information about nanomaterial-containing drugs will now be captured in CMC reviews of current and future CDER drug application submissions. This information will be entered into a nanotechnology database under construction and ultimately be used to develop policy regarding these products.

BACKGROUND

- Because development of nanotechnology-based drugs is still in its infancy, there are no established standards for the study or regulatory evaluation of these products. In response to this, the Food and Drug Administration (FDA) established the Nanotechnology Task Force, which issued a report in July 2007. This report included a series of recommendations on scientific and regulatory policy issues. Some of the recommendations highlighted the need for Center-specific guidance documents to help support the development of safe and effective nanomaterial-containing products. However, in order to develop guidance for industry, CDER needs to organize all the data submitted in support of nanotechnology-based drug applications.

- To that end, CDER's Office of Pharmaceutical Science (OPS), Science and Research Staff, started to develop a comprehensive database of products containing nanomaterials that were the subject of CDER drug applications. In developing this database, it became clear early on that much of the information that was necessary to populate the fields of the database was not being captured consistently in CMC reviews. CDER needed to establish appropriate procedures by which to effectively and efficiently track applications for products that contain nanomaterials. Consequently, CDER found it important to develop a format to help reviewers document in their reviews relevant information when an application is for a product containing nanomaterials.

REFERENCES

- MAPP 6030.1, IND Process and Review Procedures (Including Clinical Holds).
- Document Archiving, Reporting, and Regulatory Tracking System (DARRTS).
- Division File System (DFS).
- Nanotechnology: A Report of the U.S. Food and Drug Administration Nanotechnology Task Force.

DEFINITIONS[1]

- **Nanomaterial/Nanoscale Material:** Any materials with at least one dimension smaller than 1,000 nm.
- **Nanomedicine:** The use of nanoscale materials for medical applications.
- **Characterization:** Physicochemical evaluation of relevant drug properties.

RESPONSIBILITIES

- OPS CMC reviewers are responsible for adequately and correctly documenting nanotechnology-related information in their reviews of CDER drug application submissions. This information is to appear in reviews in the form of a table (see Attachment A). The purpose of employing this table is to allow for nanotechnology-related information to be presented in a standardized and searchable format.
- Secondary CMC reviewers, as well as OPS management, are responsible for ensuring that CMC reviews document in the table whether the application contains nanotechnology-related information and that the information is accurate.
- Initially, OPS's Science and Research Staff will be responsible for conducting the DARRTS/DFS searches so they can populate the nanotechnology database. Who will be responsible for maintaining the database on a permanent basis will be determined once the database is in place.

PROCEDURES

- To populate the nanotechnology database, OPS's Science and Research Staff will search CMC reviews in DARRTS/DFS using established terms (see Attachment B). If, in a CMC review for a particular drug application, the response to question 2 in the table provided in Attachment A is "Yes" (meaning that the application contains

[1] The definitions described in this section apply only to this MAPP. See Attachment B for a list of search terms that CDER is using to populate the nanotechnology database. CMC reviewers can refer to this list to identify nanomaterials in drug products.

nanomaterials), then that review will be selected and all the relevant nanotechnology-related information in that CMC review will be gathered.

- Accordingly, that information will be entered into the CDER nanotechnology drug product database. The database entry template is provided in Attachment C.

- Below is a list of the information that a CMC reviewer should document (if available) in the appropriate CMC review to allow for a better understanding of the properties of nanomaterials. (See the nanotechnology product review flow chart in Attachment D for an illustrated version of what is listed below.)

  - Whether the application contains nanomaterials.[2]

  - What type of nanomaterial is included in the product (examples of this are listed as search terms in Attachment B).

  - Whether the nanomaterial is a reformulation of a previously approved product.

  - Whether the nanomaterial is part of the drug substance (active pharmaceutical ingredient (API)) or the drug product (carrier, excipient, or packaging).

  - Whether the particle size was described in the application and what the reported particle size (average primary particle size, size range distribution, aggregation status, agglomeration status) is. With changes in formulation, it is possible that the information on particle size may change. If that is the case, the change in particle size will have to be reflected in the nanotechnology section of any subsequent review so that the most up-to-date information is available in the database.

  - Whether the techniques used to assess particle size are thoroughly described with respect to their adequacy. Attachment E provides examples of techniques that may be used to assess size, as well as examples of techniques that may be used to evaluate other nanomaterial properties. Reviewers can use their scientific judgment to determine the adequacy of the techniques used by the sponsor.

  - Whether the nanomaterial is soluble or insoluble in an aqueous environment (e.g., gold nanoparticle (insoluble) versus nanocrystal (soluble)).

  - What other properties of the nanomaterial (e.g., surface charge, surface properties) were measured and reported in the application and how those properties were measured (e.g., surface probe microscopy, laser Doppler

[2] This element must be documented.

electrophoresis). Attachment E provides a list of possible properties and methodologies that could be used to measure them.

- CMC reviewers will copy, paste, and fill in Attachment A for the CMC review in section "P.2.2.3 Physicochemical and Biological Properties (ICH-CTD-MQ4)." By placing this table in the same section of all CMC reviews, the CMC reviewers will ensure consistency and allow for more efficient searching of the reviews. Each new CMC review must contain the most up-to-date populated version of the table provided in Attachment A. If new information is not added, this must be indicated under question 1 in the table.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Attachment A: Nanotechnology Product Evaluating Questions

1) This review contains new information added to the table below: _____Yes _____No Review date: _____
2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes_____; No_____ ; Maybe (please specify)_____
3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____ 3 b) What is the source of the nanomaterial?_____
4) Is the nanomaterial a reformulation of a previously approved product? Yes_____ No_____
5) What is the nanomaterial functionality? Carrier_____; Excipient_____; Packaging_____; API_____; Other_____
6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment? Soluble _____; Insoluble_____
7) Was particle size or size range of the nanomaterial included in the application? Yes_____ (Complete 8) ; No_____(Go to 9)
8) What is the reported particle size? Mean particle size_____ ; Size distribution_____; Other_____
9) Please indicate the reason(s) why the particle size or size range was not provided: _____ _____
10) What other properties of the nanomaterial were reported in the application (see Attachment E)? _____
11) List all methods used to characterize the nanomaterial. _____

Attachment B: Search Terms for Populating the CDER Nanotechnology Drug Product Database

- **Nanotechnology:** The understanding and control of matter at dimensions between approximately 1 to 100 nanometers, where unique phenomena enable novel applications. (*Source:* National Nanotechnology Initiative Definition)

- **Nanoparticle:** Nano-object with all three external dimensions at the nanoscale that is the size range from approximately 1 nm to 100 nm. (*Source:* www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=44278; last accessed December 2008) Polymeric nanoparticle platforms are characterized by their physicochemical structures including solid nanoparticles, nanoshell, dendrimer, polymeric micelle, and polymer-drug conjugates. (*Source:* F. Alexis, et al., Factors affecting the clearance and biodistribution of polymeric nanoparticles, Mol Pharm., 2008)

- **Dendrimer:** A polymer in which the atoms are arranged in many branches and subbranches along a central backbone of carbon atoms. (*Source:* American Heritage Science Dictionary)

- **Liposomes:** Vesicles composed of one or more bilayers of amphiphatic lipid molecules enclosing one or more aqueous compartments. (*Source: Guidance for Industry: Liposome Drug Products*, August 2002; last accessed May 2008)

- **Micelles:** Self-assembling nanosized colloidal particles with a hydrophobic core and hydrophilic shell currently used for the solubilization of various poorly soluble pharmaceuticals. (*Source:* V.P. Torchilin, Lipid-core micelles for targeted drug delivery, Curr Drug Deliv., 2005)

- **Nanoemulsions:** Emulsions with droplet size in the nanometer scale. Emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases, one of which is dispersed as globules (the dispersed phase), in the other liquid phase (the continued phase), stabilized by the presence of an emulsifying agent. However, one type of emulsion—microemulsions—does demonstrate stability. (*Source:* Chapter 18: Coarse Dispersions, In A. Martin (ed.), Physical Pharmacy: physical chemical principles in the pharmaceutical sciences, 1993)

- **Nanocrystal:** Nanoscale solid formed with a periodic lattice of atoms, ions, or molecules. (*Source:* www.bsi-global.com)

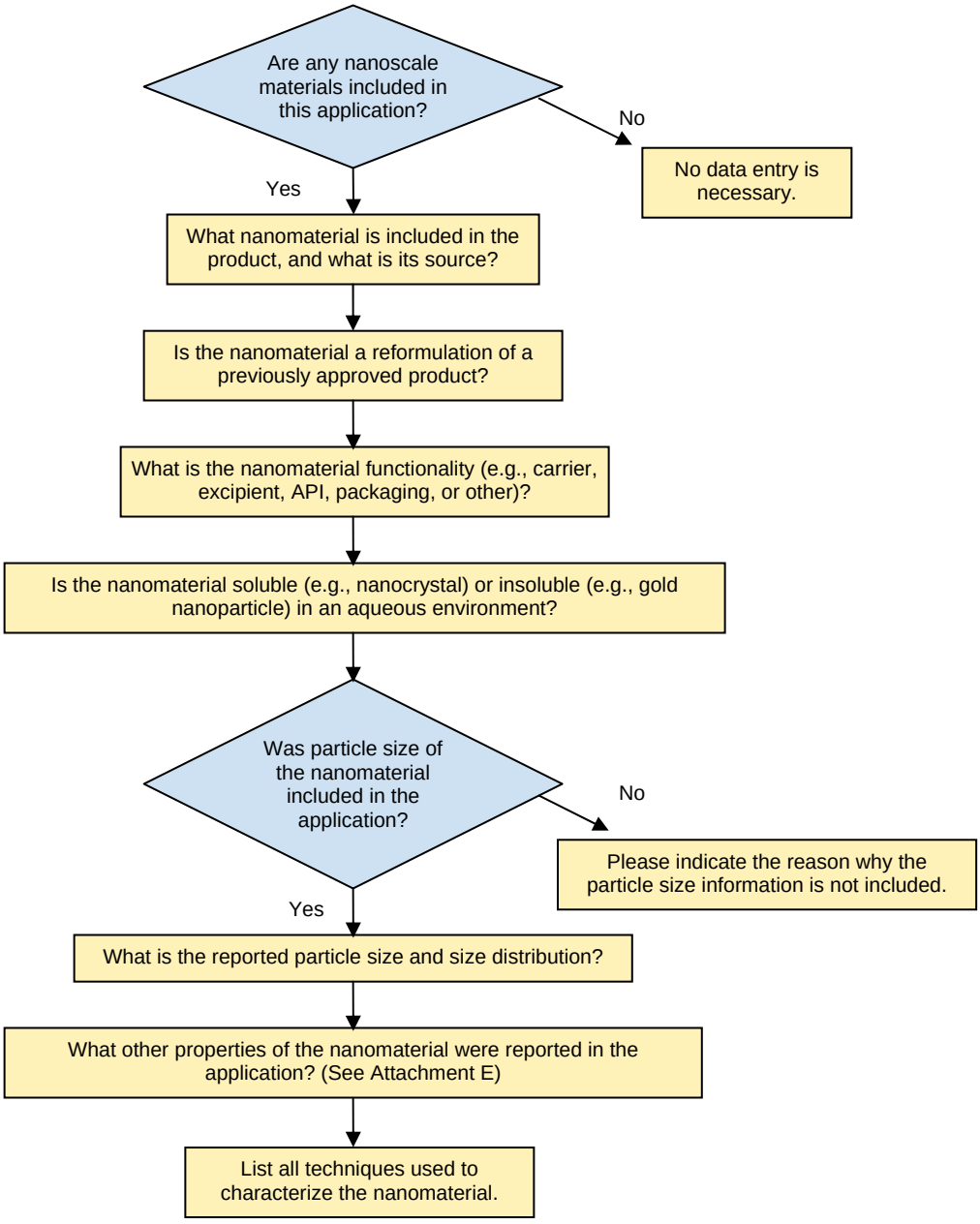
- **Primary Particle:** Smallest identifiable subdivision in a particulate system. (*Source:* www.bsi-global.com)

- **Metal Colloids:** Metal nanoparticles in colloidal systems where the term colloidal refers to a state of subdivision. This implies that the molecules or polymolecular particles are dispersed in a medium and have at least in one direction a dimension roughly between 1 nm and 1µm or, in a system, have discontinuities at distances of that order. For example, silver, gold, titanium dioxide, zinc oxide, and iron oxide. (*Source:* International Union of Pure and Applied Chemistry, Manual of Symbols and Terminology for Physicochemical Quantities and Units, 2001)

Attachment C: Template for CDER Nanotechnology Drug Product Database Entry

Comment	For any comments or QC for the data entered
ID	Database entry #
NDA/IND	NDA # and related IND #
Drug Name	Name of drug (Trade name; generic name; code name)
Description	Description of drug substance or drug product that involves nanotechnology, e.g., the drug is encapsulated within liposomes, dendrimer, or PEGylated nanoparticle, etc.
Indication	Indication of the drug, e.g., antiemetic, antineoplastic, etc.
Route of Admin	Oral, I.V., etc.
Sponsor	Name of Sponsor
Approval Date	FDA approval date
Responsible Division	Name of responsible division and HFD code
Particle Size Range	Mean particle size and particle size distribution
Technique for Assessing	Characterization technique for assessing nanospecific properties. Refer to Attachment E from the MAPP.
Search Keys	Keywords that are used to search to find nanomaterial from database, e.g., nanoparticle. Refer to Attachment B from the MAPP.
Link to Quality Reviews	Create a link to the Chemistry Reviews
Link to Clinical Reviews	Create a link to the Clinical Reviews
Link to ClinPharm Reviews	Create a link to the ClinPharm Reviews
Link to PharmTox Reviews	Create a link to the PharmTox Reviews

Attachment D: Nanotechnology Product Review Flow Chart



Attachment E: Common Techniques Used to Characterize Nanomaterials

PROPERTIES[a]	**COMMON TECHNIQUES**[b,c]
MORPHOLOGY	
Size (primary particle)	TEM, SEM, AFM, XRD
Size (primary/aggregate/agglomerate)[d]	TEM, SEM, AFM, DLS, FFF, AUC, CHDF, XDC, HPLC, DMA(1)
Size distribution	TEM, SEM, AFM, DLS, AUC, FFF, HPLC, SMA
Molecular weight	SLS, AUC, GPC
Structure/Shape	TEM, SEM, AFM, NMR
Stability (3D structure)	DLS, AUC, FFF, SEM, TEM
SURFACE	
Surface area	BET
Surface charge	SPM, GE, Titration methods
Zeta potential	LDE, ESA, PALS
Surface coating composition	SPM, XPS, MS, RS, FTIR, NMR
Surface coating coverage	AFM, AUC, TGA
Surface reactivity	Varies with nanomaterial
Surface-core interaction	SPM, RS, ITC, AUC, GE
Topology	SEM, SPM, MS
CHEMICAL	
Chemical composition (core, surface)	XPS, MS, AAS, ICP-MS, RS, FTIR, NMR
Purity	ICP-MS, AAS, AUC, HPLC, DSC
Stability (chemical)	MS, HPLC, RS, FTIR
Solubility (chemical)	Varies with nanomaterial
Structure (chemical)	NMR, XRD
Crystallinity	XRD, DSC
Catalytic activity	Varies with nanomaterial
OTHER	
Drug loading	MS, HPLC, UV-Vis, varies with nanomaterial
Drug potency/functionality	Varies with nanomaterial
In vitro release (detection)	UV-Vis, MS, HPLC, varies with nanomaterial
Deformability	AFM, DMA(2)

[a] *The property list is not definitive. Other properties may be reported.*

[b] *Only common techniques are listed. Other techniques may be valid. The choice of techniques should be justified.*

[c] *An abbreviation list and references are provided on the following page.*

[d] *These techniques will measure the average particle size, but can not necessarily distinguish between primary particles, aggregates, and agglomerates.*

ABBREVIATIONS

AAS	Atomic absorption spectroscopy	ITC	Isothermal titration calorimetry
AFM	Atomic force microscopy	LDE	Laser doppler electrophoresis
AUC	Analytical ultracentrifugation	MS	Mass spectrometry (GCMS, TOFMS, SIMS, etc.)
BET	Brunauer, Emmett, and Teller method	NMR	Nuclear magnetic resonance
CHDF	Capillary hydrodynamic fractionation	PALS	Phase analysis light scattering
DLS	Dynamic light scattering	RS	Raman spectroscopy
DMA(1)	Differential mobility analyzer	SEM	Scanning electron microscopy
DMA(2)	Dynamic mechanical analyzer	SLS	Static light scattering
DSC	Differential scanning calorimetry	SMA	Scanning mobility particle sizer
ESA	Electroacoustic spectroscopy	SPM	Surface probe microscopy (AFM, STM, NSOM, etc.)
FFF	Field flow fractionation	TEM	Transmission electron microscopy
FTIR	Fourier transform infrared spectroscopy	TGA	Thermal gravimetric analysis
GE	Gel electrophoresis	UV-Vis	Ultraviolet-visible spectrometry
GPC	Gel permeation chromatography	XDC	X-ray disk centrifuge
HPLC	High performance liquid chromatography	XPS	X-ray photoelectron spectroscopy
ICP-MS	Inductively coupled plasma mass spectrometry	XRD	X-ray diffraction

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